Thyroid stimulating hormone, free thyroxine and cognitive ability in old age

Thyroid Stimulating Hormone, Free Thyroxine and Cognitive Ability in Old Age: The Lothian Birth Cohort Study 1936.

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Abstract

The current study investigated the associations between thyroid stimulating hormone (TSH), free thyroxine (T_4) and cognitive ability (general ability, memory and processing speed), in a large age homogenous sample (n=659) of generally healthy euthyroid older adults. Associations were considered both at baseline (Mean Age Wave 1=69.5 years; SD=0.8 years) and approximately 3 years later (Mean Age Wave 2=72.5 years; SD=0.7 years). Results indicated mean level decreases across waves in both TSH (t=10.99, $p<0.001$) and T_4 (t=34.55, $p<0.001$). There were no significant associations between TSH and T_4 with any of the cognitive variables at either wave. There was no suggestion of non-linear associations. The lack of associations supports suggestions that the effects of thyroid hormones on cognition may be restricted to older individuals above a given threshold, and/or those with levels of thyroid hormones within the range defining clinical thyroid disorder.

Keywords: Thyroid Stimulating Hormone; TSH; Free Thyroxine; T_4; Cognitive Ability; Memory; Processing Speed.

1. Introduction

The maintenance of cognitive abilities into later life is a key determinant of a wide variety of positive life outcomes and successful ageing (Deary, 2012). Thyroid function is mooted to be important for the development and retention of cognitive function (Begin et al., 2008), with thyroid dysfunction, most commonly clinical and subclinical hypothyroidism, in later life being associated with both dementia and, more specifically, Alzheimer disease (Smith et al., 2002; Liesbeth et al., 2012). As a result, there is growing interest in whether thyroid hormones at both normal and clinical levels, are associated with cognitive performance across the life span. However, research has failed to show consistent associations between cognitive abilities and thyroid function in samples of generally healthy elderly subjects with subclinical thyroid dysfunction.

For example, St. John et al. (2009) found no association between TSH levels and cognitive ability in a sample of 489 men and women (mean age = 60.5 years). Roberts et al. (2007) found no significant differences in Mini-Mental State Exam (MMSE) or Middlesex Elderly Assessment of Mental State (MEAMS) scores between individuals with subclinical thyroid disorders and euthyroid from a large cross-sectional sample (Birmingham Elderly Thyroid Study; n=5685, age = >65 years). Higher TSH was associated with higher MMSE scores, but not to MEAMS score. Using a subsample of the same cohort in a randomized controlled trial, Parle et al (2010) found no significant differences between the placebo group (n=42, mean age 74.2 years) and a group receiving T_4 hormone treatment (n=52, mean age 73.5years) in any cognitive measures. Similarly, in a follow up study of 599 older individuals (85 through 89 years), Gussekloo et al (2004) found no associations between TSH, T_3 or T_4 and cognitive functioning. Hogervorst et al. (2008) found that after controlling for the presence thyroid disease, stroke and dementia, higher normal T_4 was associated with lower MMSE scores at baseline, and a greater risk of decline across 2 years, in a sample of 1047 older adults (mean

age at baseline 73.6 years). Conversely, using the NHANES III sample, Beydoun et al. (2012) found that higher levels of thyroxine, TSH were associated with improved cognitive performance on a math test, and a story recall test, in the 60 to 90 years age group (n=5989 and 5878 respectively).

Begin et al. (2008) reporting on five previously published studies of euthyroid samples concluded that, from the mixed results; that it is unclear whether Thyroid Stimulating Hormone (TSH), tri-iodothyronine (T_3) or free thyroxine (T_4) is the most relevant associate of cognitive function; and that the only consistent cognitive association was with memory impairment across all biomarkers. A similar conclusions is reached from the nine studies reviewed by Hogervorst et al (2008; see Table 1, p.1014), in which four studies found some degree of significant association between memory and thyroid hormone levels in older samples (age range across studies 49 to 89).

In totality, results from prior studies have been inconsistent, and provide little evidence for associations between thyroid hormones and cognitive ability in generally healthy older adults. Samuels (2010), in reviewing the general lack of associations found in studies of subclinical hypothyroidism, noted that: a) few studies report on the largely more sensitive T_4 measurements (although for impaired thyroid function TSH might be preferred); and b) most studies rely on cognitive assessments designed to identify gross impairment (e.g. MMSE or MEAMS). Such measures may be insensitive to changes in cognitive function within the normal range of abilities.

In the current study we investigate the associations between TSH, T_4 and major domains of cognitive ability assessed using widely validated psychometric tools, in a large age-homogeneous sample of generally healthy older adults.

2. Methods

2.1 Sample

The current sample is drawn from the Lothian Birth Cohort Study 1936 (LBC1936), a longitudinal study of ageing. Full information on the recruitment and testing of participants has been previously published in study protocols and profile (Deary et al., 2007; Deary et al., 2011). In short, surviving members of the Scottish Mental Health Survey 1947 (SMS1947) resident in Edinburgh and the surrounding Lothian area, were recruited between June 2004 and November 2006.

In total, 1091 participants took part in wave 1 of testing where they completed a wide array of psychometric tests, a physical examination entailing a number of tests of physical functioning (6 metre walk, stand-sit test, grip strength, blood pressure etc.). Blood samples were also taken as part of the physical examination. At wave 2, 866 participants returned approximately three years later and repeated largely the same array of cognitive, psychometric, and physical tests. In the present study, we included participants who (n indicating the numbers who meet inclusion criteria at each step);

Completed both waves 1 and 2 (n=866).

Had complete data for TSH and T_4 (n=810).

Did not report any thyroid disease at both waves 1 and 2 (n=711).

Scored ≥24 on the Mini-Mental State Exam (Folstein et al., 1975), as lower scores are often considered to be a marker of cognitive impairment (n=701).

Had TSH levels within the range of 0.2 to 4.5 mU/l at both waves 1 and 2 (n=660).

Had T_4 levels with the range of 9 to 21 pmol/L waves 1 and 2 (n=659).

Applying these criteria resulted in a final sample of 659 (male=371; female=288; Mean age Wave 1=69.5 years, SD=0.8 years; Mean age wave 2=72.5 years, SD=0.7 years) participants for the current analyses.

2.2 Ethical Considerations

Ethical permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland and the Lothian Research Ethics Committee. All research was carried out in compliance with the Helsinki Declaration.

2.3 TSH and T_4

Blood samples were taken at both waves 1 and 2. All analyses were conducted in the same laboratory (NHS Lothian –Clinical Biochemistry & Haematology, Western General Hospital, UK) using a two-step immunoassay. Target precision of both the TSH and T_4 assays were coefficient of variability <10%.

For TSH, the laboratory reference range was 0.2 to 4.5 mU/l, with coefficients of variability ranging from 3.0 to 3.5%. For T_4, the laboratory reference range was 9 to 21 pmol/L, with coefficients of variability ranging from 5.1 to 8.9%.

In the current study we use the laboratory reference range as a selection criterion. This reference range has been used in other published work on different samples (Patterson, Lonie and Starr, 2010).

2.4 Cognitive Ability Tests

In the current study we used 14 cognitive ability subscale scores from 12 individual cognitive tests. General cognitive ability (g) was measured using 6 subtest scores of the WAIS-III^{UK} (Wechsler, 1998a; Block Design, Matrix Reasoning, Digit Span Backward, Digit Symbol, Symbol Search and Letter-Number Sequencing). Processing Speed was measured using two timed WAIS-III^{UK} subtest scores (Digit Symbol and Symbol Search), a simple and choice reaction time task, and an inspection time task. Lastly, Memory was measured using five subtest scores from the WMS-III^{UK} (Wechsler, 1998b; Logical Memory Immediate and delayed recall, Verbal Paired Associates immediate and delayed recall and Spatial Span total score) and two scores from the WAIS-III^{UK}, Digit Span Backward and Letter-Number Sequencing.

2.5 Statistical Analysis

Means, standard deviations, skew and kurtosis were computed for all raw data. Pearsons correlations between individual subtest scores, TSH and T_4 at both waves 1 and 2 were computed. Next, we used structural equation modelling (SEM) to estimate the cross-lagged correlations between three latent cognitive ability variables (*g,* processing speed, and memory) and TSH and T_4 measures at both waves 1 and 2. The latent factors represent the shared associations between individual cognitive ability subtest scores hypothesized to measure the same major domain of cognitive ability. SEM provides highly reliable estimates of broad cognitive domains by taking account of measurement error present in each subtest. All models were estimated in Mplus 6.0 using full information maximum likelihood estimation. Full details of the structural models can be found in Supplementary Material A. Lastly, we produced scatterplots with fitted loess curves of latent variable estimates in order to consider non-linear effects (see Supplementary Material B).

2.6 Covariates

All models were estimated both with and without the inclusion of health covariates. Participants' smoking status (former/current/never), alcohol consumption (drink/not drink), history (yes/no) of diabetes, hypertension, high cholesterol, cardiovascular disease, circulatory problems and stroke, were gathered from a medical interview. In addition we included the depression subscale score from the self-report Hospital Anxiety and Depression scale (HADS: Zigmond and Snaith, 1983).

In order to assess potential effects of BMI and medications known to effect thyroid hormone levels we re-ran all models excluding firstly participants with BMI less than 20 (n=18), and secondly those taking any of the following medications; hydrocortisone, prednisolone, growth hormone, octreotide, somatostatin, morphine, dihydrocodeine, tramadol, dopamine, L-dopa, madopar, sinemet, pimozide, phenotolamine, thioridazine,

methysergide, cyproheptadine, iodine, lithium, ropinerole, pramipexole, cabergoline, iodide or amiodarone (n=24).

3. Results

3.1 Descriptive Statistics

Full descriptive statistics are presented in Table 1. All variables were approximately normally distributed with no values for skew outside of ±1.99. Across the waves, there were significant mean level decreases in both TSH (t=10.99, $p<0.001$) and T_4 (t=34.55, $p<0.001$).

(Insert Table 1 about here)

Univariate correlations between individual cognitive subtests and thyroid hormones at waves 1 and 2 yielded few significant results (for full table see Supplementary Material C). Digit Span Backwards (-0.09), Letter-Number Sequencing (-0.08) and Simple Reaction Time (0.12) were significantly associated with TSH levels at wave 1, but not at wave 2. Conversely, Block Design (-0.10) and Simple Reaction Time (0.10) were significantly associated with T_4 levels at wave 2, but not wave 1. In totality, few systematic associations were present in the current sample.

Estimates of the associations between TSH or T_4 levels and *g,* processing speed and memory derived from cross-lagged latent variable structural models are presented in Table 2. All structural models showed excellent fit to the data (see Supplementary Material A). No significant associations were found between either TSH or T_4 and any of the cognitive measures.

(Insert Table 2 about here)

All changes to parameter estimates removing cases with low BMI were at the second decimal place, with all values remaining non-significant. Similarly, all changes in parameter estimates were at the second decimal place in the models excluding participants currently taking potentially confounding medications (see Supplementary Material D for raw results). In this

model, the association between T_4 at wave 1 and Memory at wave 2 was significant (0.10, $p<0.05$). However, given the large number of parameters estimated we suggest this is simply a Type 1 error.

Scatterplots were produced plotting the latent factor scores of each cognitive ability factor against TSH and T_4 at both waves. The scatterplots provided no indication of non-linear associations (see Supplementary Material B).

4. Discussion

In the current euthyroid sample, we found no significant associations between thyroid function as measured by TSH and T_4 and three major domains of cognitive ability (g, memory and processing speed). Further, we found no evidence of non-linear associations. These conclusions hold true both with and without controlling for a large number of health covariates, as well as when analyses were re-run excluding those on medications and with low BMI. Notably, both TSH and T_4 levels decreased over the three year follow-up period consistent with a fall in thyrotropin-releasing hormone (TRH), although we did not measure this directly. Although there are several cross-sectional studies that have found lower TRH levels in older participants, there is a paucity of longitudinal data (Leitol et al., 2002).

These findings support suggestions from previous studies in which the authors have suggested that thyroid-cognition associations may only be present at clinical levels of thyroid dysfunction (Begin et al. 2008; St. John et al. 2009). The association between thyroid hormone levels and memory ability was identified as perhaps the most consistent finding from past research (e.g. Begin et al. 2008; Hogervorst et al. 2008). Again in the current study, we found no support for this association.

However, the current study offers a number of important extensions to prior studies. Firstly, we use a multiple cognitive tests to identify latent cognitive ability factors of g, processing speed, and memory, and thus, provide robust estimates from structural equation models.

Secondly, we were able to estimate the associations in the same large sample (n=659) at baseline and with an approximate three year follow up. Given this sample size, the current study was powered to identify correlations of approximately 0.11 (n=659; 80% power; $p<.05$), which is a small effect size. As a result, we consider the current findings to be highly robust.

Lastly, the cohort design and narrow age range of the current sample provided almost eliminated the effect of chronological age, which otherwise could have been a major confounder of any effects of thyroid hormone levels on cognition. A number of authors have suggested that the major impact of thyroid levels on cognition occurs above a key threshold of ~80 years of age (van den Beld et al., 2005; Begin et al., 2008). If such a threshold exists, then the current sample would be too young for the major effects of thyroid function to be impacting on cognitive performance. However, given the consistency of the current results with prior findings, it is suggested they are indicative of a lack of association within the normal ranges of TSH and T_4.

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Table 1: Means, Standard Deviations, Skew and Kurtosis for all variables

	Wave 1				Wave 2			
	Mean	SD	Skew	Kurt.	Mean	SD	Skew	Kurt.
WAIS-III^{UK}								
Digit Symbol	57.87	12.83	0.10	-0.02	56.74	12.17	0.08	-0.19
Digit Span Backwards	7.86	2.28	0.45	-0.24	7.86	2.23	0.33	-0.09
Block Design	34.87	10.09	0.19	-0.21	34.15	10.14	0.43	0.09
Letter-Number Sequencing	11.15	3.06	0.12	-0.07	11.02	3.02	0.35	0.45
Matrix Reasoning	14.02	5.05	-0.13	-0.96	13.36	5.00	-0.10	-1.02
Symbol Search	25.23	6.33	-0.04	0.86	24.97	5.95	-0.32	0.90
WMS-III^{UK}								
Logical Memory Immediate	45.05	9.90	-0.34	-0.11	46.12	10.06	-0.38	0.14
Logical Memory Delayed	28.17	7.63	-0.36	-0.07	29.17	7.76	-0.53	0.30
Verbal Paired Associates Immediate	2.60	2.17	0.82	-0.17	2.77	2.23	0.65	-0.55
Verbal Paired Associates Delayed	6.31	1.93	-1.03	0.18	6.39	2.02	-1.33	0.99
Spatial Span	14.88	2.82	0.05	-0.23	14.77	2.70	-0.10	-0.03
Speed Tests								
Simple Reaction Time	0.27	0.05	1.99	6.57	0.27	0.05	1.50	3.06
Choice Reaction Time	0.63	0.08	1.02	2.81	0.65	0.09	0.82	1.35
Inspection Time	112.99	11.23	-0.90	2.70	111.91	11.76	-1.06	2.58
Thyroid Hormones								
TSH	1.82	0.88	0.82	0.26	1.57	0.76	1.02	1.18
T_4	15.29	2.04	0.12	0.05	12.65	1.58	0.22	-0.12

Table 2:

Cross-lagged Correlations between Cognitive Ability Latent Variables, TSH and T_4

	1	2	3	4	5	6	7	8	9	10
1. TSH Wave 1	-	**0.76**	-	-	-0.06	-0.06	-0.05	-0.07	-0.08	-0.07
2. TSH Wave 2	**0.76**	-	-	-	-0.02	0.00	-0.04	-0.06	-0.03	-0.01
3. T_4 Wave 1	-	-	-	**0.47**	0.02	0.01	0.05	0.05	-0.01	0.07
4. T_4 Wave 2	-	-	**0.43**	-	-0.01	-0.01	-0.05	-0.02	0.04	0.02
5. g Wave 1	-0.06	-0.04	0.07	-0.05	-	**0.99**	-	-	-	-
6. g Wave 2	-0.05	-0.01	0.04	-0.06	**0.98**	-	-	-	-	-
7. Processing Speed Wave 1	-0.05	-0.06	0.05	0.05	-	-	-	**0.98**	-	-
8. Processing Speed Wave 2	-0.07	-0.07	-0.04	-0.03	-	-	**0.98**	-	-	-
9. Memory Wave 1	-0.07	-0.05	0.04	0.02	-	-	-	-	-	**0.89**
10. Memory Wave 2	-0.07	-0.03	0.09	0.02	-	-	-	-	**0.86**	-

Note: All estimates shown in bold type are the wave 1 to wave 2 stability coefficients, all significant at $p<0.001$. All other estimates are the associations between TSH, T_4 and cognition, all non-significant ($p>0.05$). Estimates below the diagonal are uncorrected. Estimates above the diagonal are corrected for sex, age, health variables and depression scores.

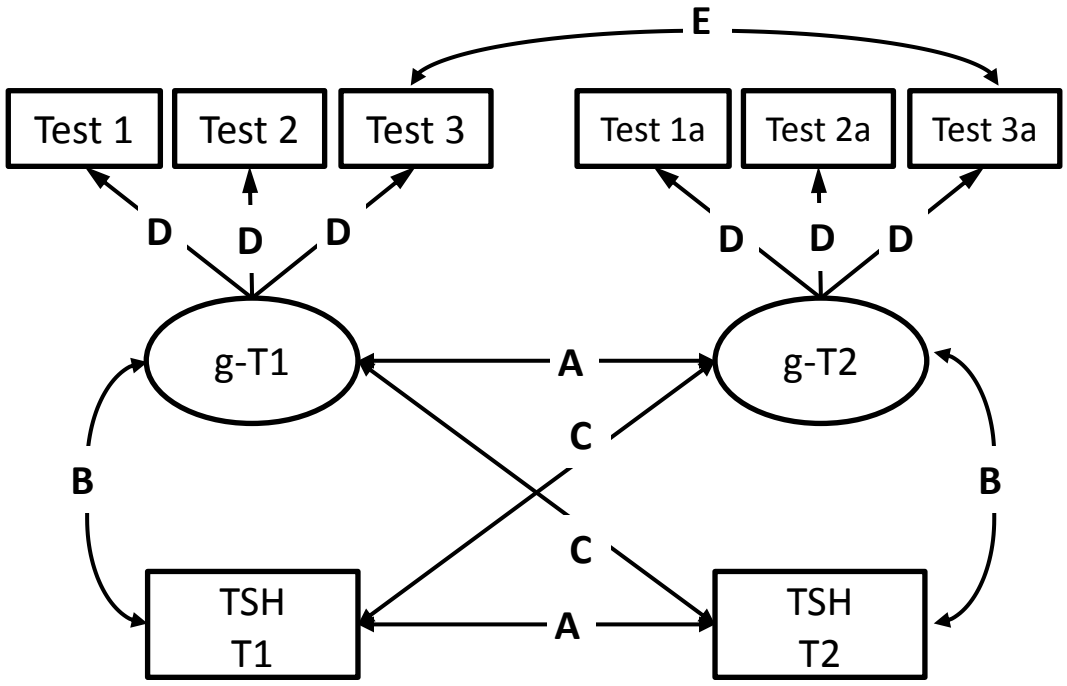
Supplementary Material A

Model Specification

The basic cross-lagged model is shown in Supplementary Figure 1. The cross-lagged model comprises six primary correlations, namely, two stability coefficients (Paths A), two contemporaneous associations within time points (Paths B) and two cross-lagged associations across time points (T1/T2; Paths C). In the current models, we modelled latent estimates for the cognitive ability factors at both waves, loaded by individual sub test scores (Paths D). In addition, we included correlation residuals (Paths E) between sub-test scores from the same testing procedure (e.g. logical memory immediate and delayed recall), and between the same sub-tests across waves 1 and 2.

Figure S1:

Cross-lagged Model Design



Model Fit

Model fit was assessed based on standard cut-off criteria (Hu & Bentler, 1998; 1999; Schermelleh-Engel, Moosbrugger, & Muller, 2003) for a number of commonly used model fit indices. We adopted cut-off's of ≥ 0.95 for the comparative fit index (CFI) and Tucker-Lewis index (TLI), values ≤ 0.06 for the root-mean-square error of approximation (RMSEA) and finally values of ≤ 0.05 for the standardised root mean square residual (SRMR). As can be seen from the results in Table S2, all models met the criteria for model fit, indicating that the parameters in the model represent a good fit to the data and can be reliably interpreted.

Table S2: Model fit statistics for the 12 cross-lagged models.

	χ^2	df	Sig.	RMSEA	SRMR	CFI	TLI
g & TSH	83.88	55	$p<0.05$	0.028	0.024	0.99	0.99
g & T_4	73.63	55	$p=0.05$	0.023	0.023	1.00	0.99
g & TSH with covariates	438.85	305	$p<0.05$	0.026	0.034	0.97	0.97
g & T_4 with covariates	422.38	305	$p<0.05$	0.024	0.033	0.98	0.97
Processing Speed & TSH	70.25	41	$p<0.05$	0.033	0.029	0.99	0.99
Processing Speed & T_4	62.47	41	$p<0.05$	0.028	0.026	0.99	0.99
Processing Speed & TSH with covariates	332.78	225	$p<0.05$	0.027	0.035	0.97	0.97
Processing Speed & T_4 with covariates	313.65	225	$p<0.05$	0.025	0.033	0.98	0.97
Memory & TSH	200.53	81	$p<0.05$	0.047	0.052	0.98	0.97
Memory & T_4	181.33	81	$p<0.05$	0.043	0.048	0.98	0.97
Memory & TSH with covariates	576.00	373	$p<0.05$	0.029	0.037	0.97	0.96
Memory & T_4 with covariates	550.06	373	$p<0.05$	0.027	0.036	0.97	0.96

Model Parameter Estimates

Tables S3, S4 and S5 display the unstandardized and standardized parameter estimates for the two wave measurement models for each of cognitive ability latent constructs. In all cases the estimates were taken from the TSH models without covariates. Measurement parameters showed negligible changes (second decimal place) in both the T_4 models, with and without covariates.

In all tables, the following abbreviations are used; <-> = Correlation; W1 = Wave 1; W2= Wave 2; DS = Digit Symbol; SS = Symbol Search; MR = Matrix Reasoning; BD = Block Design; LN = Letter-Number Sequencing; DB = Digit Span Backward; CRT = Choice Reaction Time Mean Score; SRT = Simple Reaction Time Mean Score; IT = Inspection Time Total Score; LM1 = Logical Memory Immediate Recall; LM2 = Logical Memory Delayed Recall; VPA1 = Verbal Paired Associated Immediate Recall; VPA2 = Verbal Paired Associates Delayed Recall; SP = Spatial Span Total Score.

Table S3: Parameter Estimates for the g Measurement Model

	Unstandardized	SE	Standardized	SE	Sig
Wave 1 g Loadings					
DS_W1	7.368	0.568	0.574	0.037	$p<0.001$
SS_W1	4.271	0.266	0.675	0.032	$p<0.001$
MR_W1	3.19	0.222	0.632	0.036	$p<0.001$
BD_W1	6.685	0.429	0.664	0.033	$p<0.001$
LN_W1	1.821	0.129	0.592	0.034	$p<0.001$
DB_W1	1.136	0.098	0.498	0.037	$p<0.001$
Correlated Residuals – Wave 1 Similar Tests					
DS_W1 <-> SS_W1	17.147	3.032	0.349	0.046	$p<0.001$
MR_W1 <-> BD_W1	6.361	1.872	0.216	0.054	$p<0.001$
LN_W1 <-> DB_W1	1.543	0.247	0.315	0.041	$p<0.001$
Wave 2 g Loadings					
DS_W2	7.390	0.535	0.606	0.036	$p<0.001$
SS_W2	3.835	0.254	0.644	0.034	$p<0.001$
MR_W2	2.885	0.222	0.578	0.037	$p<0.001$
BD_W2	6.601	0.435	0.652	0.034	$p<0.001$
LN_W2	1.699	0.128	0.562	0.035	$p<0.001$
DB_W2	1.041	0.097	0.466	0.038	$p<0.001$
Correlated Residuals – Wave 2 Similar Tests					
DS_W2 <-> SS_W2	15.793	2.751	0.358	0.045	$p<0.001$
MR_W2 <-> BD_W2	6.41	1.847	0.205	0.051	$p<0.001$
LN_W2 <-> DB_W2	1.814	0.247	0.367	0.038	$p<0.001$
Correlated Residuals – Same Tests Across Waves					
DS_W1 <-> DS_W2	79.846	6.818	0.784	0.018	$p<0.001$
MR_W1 <-> MR_W2	7.041	0.984	0.441	0.04	$p<0.001$
LN_W1 <-> LN_W2	2.809	0.336	0.453	0.036	$p<0.001$
SS_W1 <-> SS_W2	8.636	1.4	0.406	0.045	$p<0.001$
BD_W1 <-> BD_W2	32.98	4.013	0.571	0.035	$p<0.001$
DB_W1 <-> DB_W2	2.066	0.199	0.53	0.031	$p<0.001$
Correlates Residuals – Similar Tests Across Waves					
DS_W1 <-> SS_W2	16.421	2.851	0.343	0.045	$p<0.001$
SS_W1 <-> DS_W2	14.061	2.838	0.311	0.048	$p<0.001$
MR_W1 <-> BD_W2	4.39	1.835	0.146	0.055	$p<0.01$
BD_W1 <-> MR_W2	8.66	1.837	0.282	0.048	$p<0.001$
LN_W1 <-> DB_W2	1.215	0.239	0.248	0.042	$p<0.001$
DB_W1 <-> LN_W2	1.509	0.243	0.306	0.04	$p<0.001$

Table S4: Parameter Estimates for the Processing Speed Measurement Model

	Unstandardized	SE	Standardized	SE	Sig
Wave 1 Speed Loadings					
DS_W1	-10.21	0.467	-0.795	0.022	p<0.001
SS_W1	-4.64	0.236	-0.733	0.025	p<0.001
CRT_W1	0.053	0.003	0.639	0.028	p<0.001
SRT_W1	0.016	0.002	0.323	0.039	p<0.001
IT_W1	-4.722	0.474	-0.42	0.037	p<0.001
Correlated Residuals – Wave 1 Similar Tests					
CRT_W1 <-> SRT_W1	0.001	0.000	0.299	0.039	p<0.001
Wave 2 Speed Loadings					
DS_W2	9.899	0.439	0.81	0.021	p<0.001
SS_W2	4.45	0.222	0.745	0.024	p<0.001
CRT_W2	-0.056	0.003	-0.651	0.027	p<0.001
SRT_W2	-0.015	0.002	-0.31	0.04	p<0.001
IT_W2	6.212	0.474	0.528	0.033	p<0.001
Correlated Residuals – Wave 2 Similar Tests					
CRT_W2 <-> SRT_W2	0.001	0.000	0.375	0.036	p<0.001
Correlated Residuals – Same Tests Across Waves					
DS_W1 <-> DS_W2	34.946	4.566	0.627	0.037	p<0.001
SS_W1 <-> SS_W2	4.685	1.037	0.273	0.049	p<0.001
CRT_W1 <-> CRT_W2	0.002	0.000	0.59	0.029	p<0.001
SRT_W1 <-> SRT_W2	0.001	0.000	0.472	0.031	p<0.001
IT_W1 <-> IT_W2	56.46	4.958	0.553	0.029	p<0.001
Correlates Residuals – Similar Tests Across Waves					
SRT_W1 <-> CRT_W2	0.001	0.000	0.201	0.041	p<0.001
CRT_W1 <-> SRT_W2	0.001	0.000	0.251	0.04	p<0.001

Table S5: Parameter Estimates for the Memory Measurement Model

	Unstandardized	SE	Standardized	SE	Sig
Wave 1 Memory Loadings					
LM1_W1	6.122	0.476	0.616	0.041	p<0.001
LM2_W1	4.998	0.36	0.653	0.039	p<0.001
VPA1_W1	1.031	0.101	0.473	0.041	p<0.001
VPA2_W1	1.151	0.088	0.589	0.038	p<0.001
LN_W1	1.572	0.149	0.516	0.044	p<0.001
SP_W1	1.012	0.135	0.358	0.045	p<0.001
DB_W1	0.914	0.109	0.405	0.045	p<0.001
Correlated Residuals – Wave 1 Similar Tests					
LM1_W1 <-> LM2_W1	35.253	3.784	0.776	0.022	p<0.001
VPA1_W1 <-> VPA2_W1	1.259	0.172	0.415	0.04	p<0.001
LN_W1 <-> DB_W1	2.043	0.29	0.379	0.04	p<0.001
Wave 2 Memory Loadings					
LM1_W2	7.49	0.458	0.743	0.036	p<0.001
LM2_W2	5.802	0.354	0.746	0.036	p<0.001
VPA1_W2	1.136	0.099	0.508	0.038	p<0.001
VPA2_W2	1.214	0.089	0.595	0.036	p<0.001
LN_W2	1.473	0.141	0.49	0.042	p<0.001
SP_W2	0.943	0.125	0.349	0.044	p<0.001
DB_W2	0.829	0.103	0.374	0.043	p<0.001
Correlated Residuals – Wave 1 Similar Tests					
LM1_W2 <-> LM2_W2	24.68	3.979	0.707	0.036	p<0.001
VPA1_W2 <-> VPA2_W2	1.217	0.172	0.385	0.04	p<0.001
LN_W2 <-> DB_W2	2.278	0.273	0.422	0.036	p<0.001
Correlated Residuals – Same Tests Across Waves					
LM1_W1 <-> LM1_W2	27.366	4.216	0.518	0.043	p<0.001
LM2_W1 <-> LM2_W2	14.669	2.497	0.489	0.046	p<0.001
VPA1_W1 <-> VPA1_W2	1.933	0.192	0.522	0.032	p<0.001
VPA2_W1 <-> VPA2_W2	1.425	0.154	0.55	0.034	p<0.001
LN_W1 <-> LN_W2	3.657	0.385	0.534	0.032	p<0.001
SP_W1 <-> SP_W2	3.421	0.32	0.512	0.03	p<0.001
DB_W1 <-> DB_W2	2.443	0.215	0.575	0.028	p<0.001
Correlates Residuals – Similar Tests Across Waves					
LM1_W1 <-> LM2_W2	18.166	3.203	0.449	0.048	p<0.001
LM2_W1 <-> LM1_W2	17.598	3.2	0.449	0.049	p<0.001
VPA1_W1<-> VPA2_W2	0.88	0.16	0.279	0.043	p<0.001
VPA2_W1 <-> VPA1_W2	1.006	0.159	0.33	0.042	p<0.001
LN_W1 <-> DB_W2	1.795	0.264	0.334	0.039	p<0.001
DB_W1 <-> LN_W2	2.062	0.271	0.381	0.038	p<0.001

Supplementary Material B

In order to investigate whether the lack of significant associations was due to the linearity assumptions of correlation coefficients, we produced scatter-plots of the latent factor scores for the cognitive ability variables derived from the structural equation models, against TSH and T4 levels at both waves 1 and 2 (Total 24 plots). Next we fitted loess curves to the scatterplots. Loess curves are generated by locally fitting points along the x-axis, with the curve created with these points are joined (Jacoby, 1997).

For illustrative purposes, figures S2 to S25 display all plots. As can be seen from these plots, no consistent and significant non-linearity is present in the current data.

Figure S2:

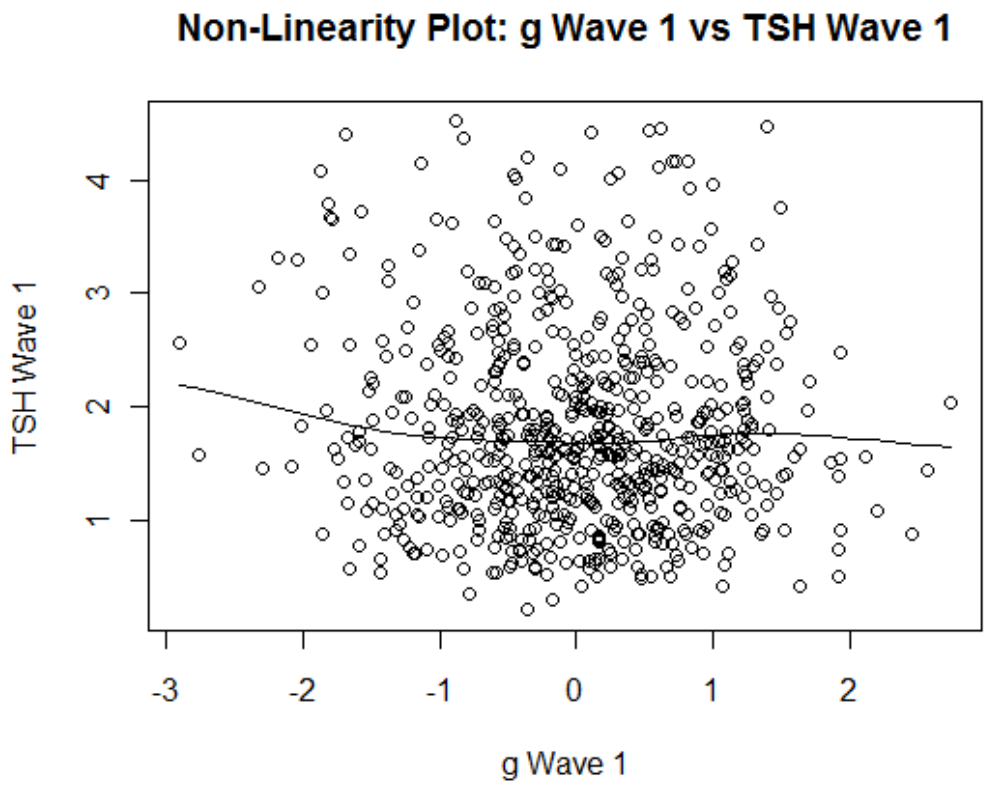


Figure S3:

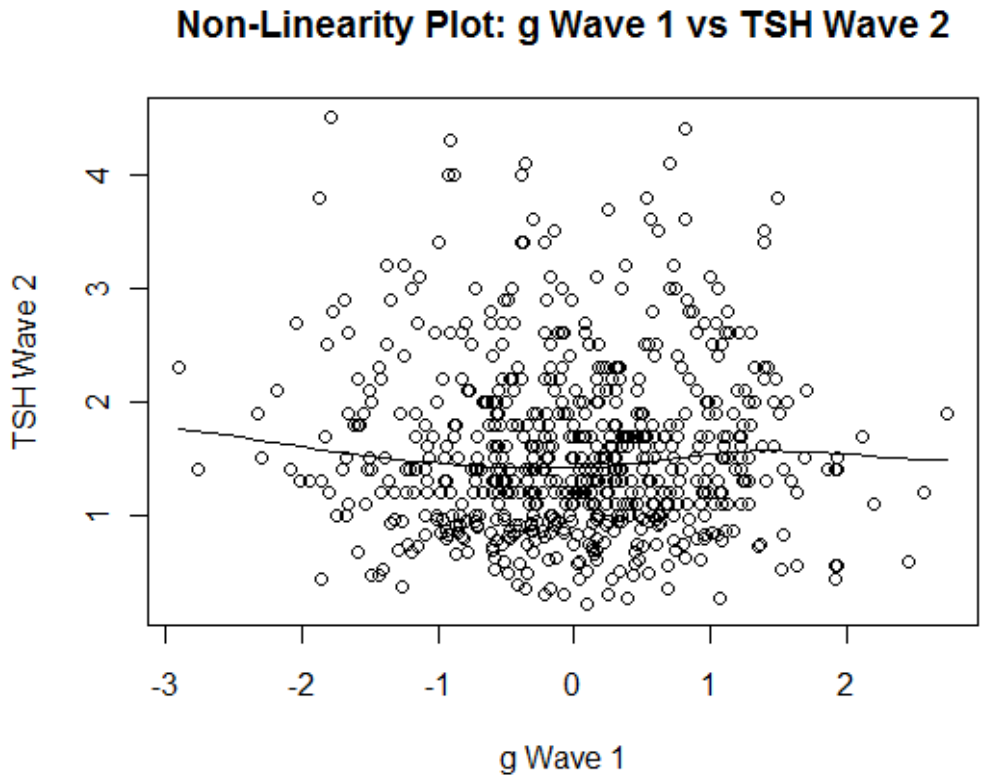


Figure S4:

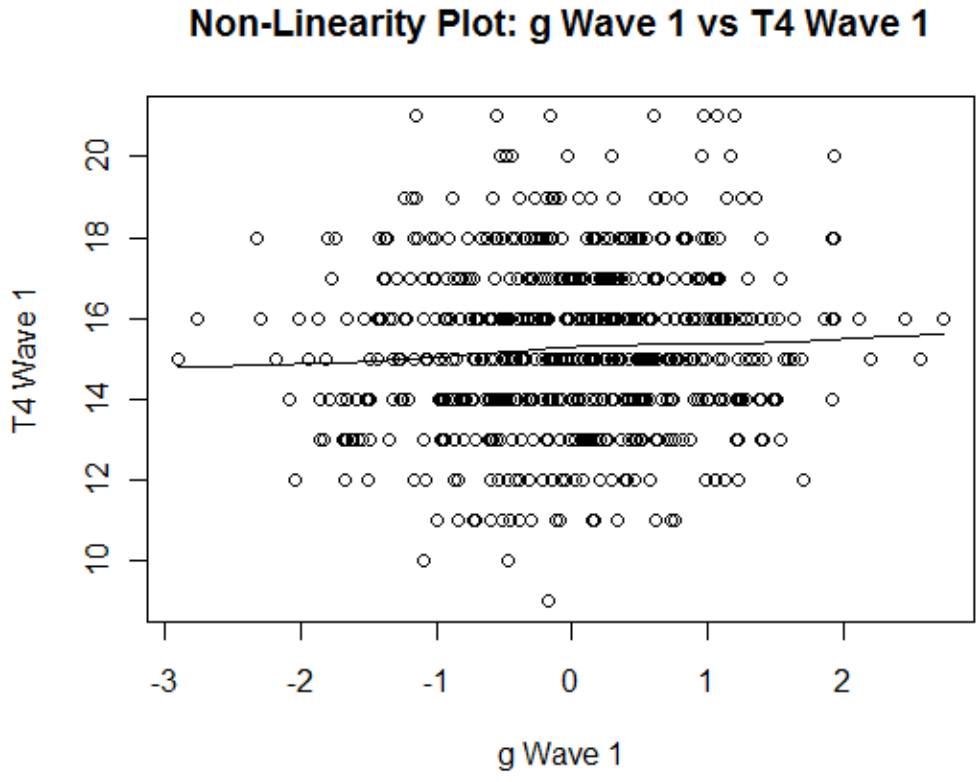


Figure S5:

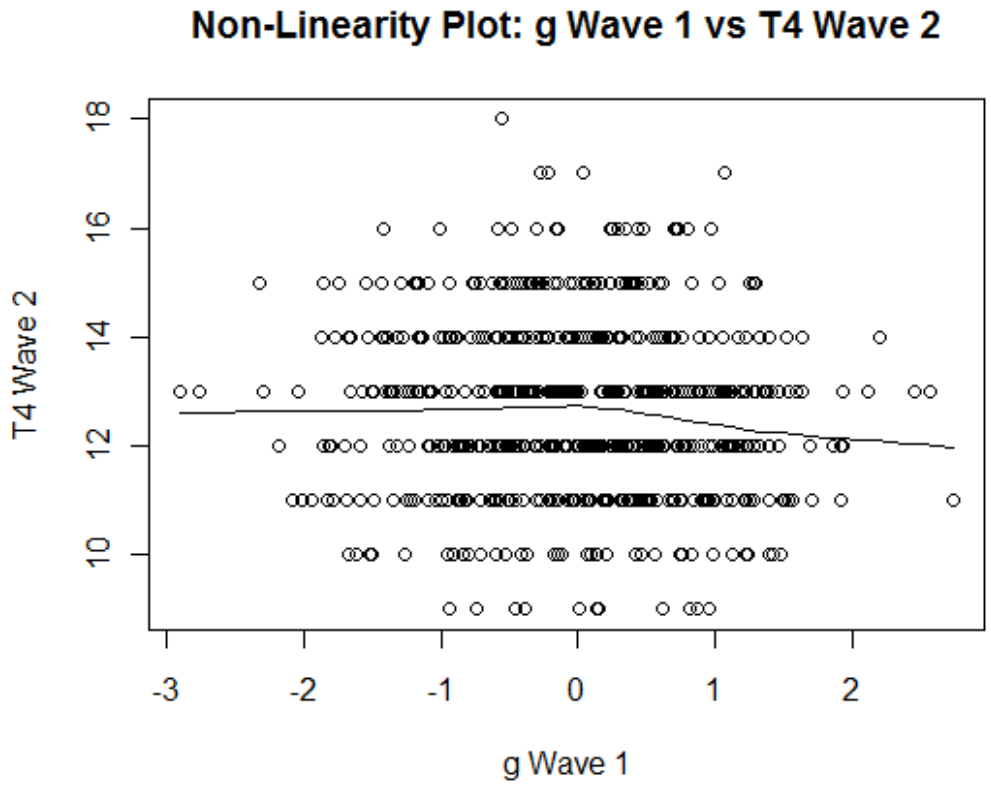


Figure S6:

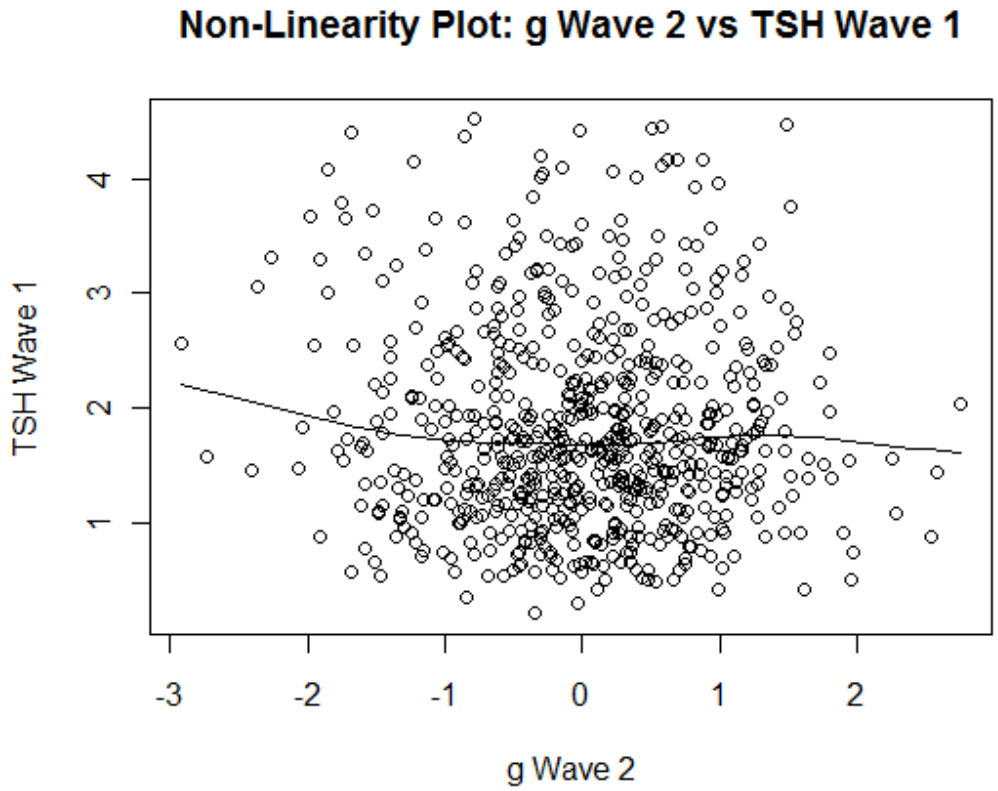


Figure S7:

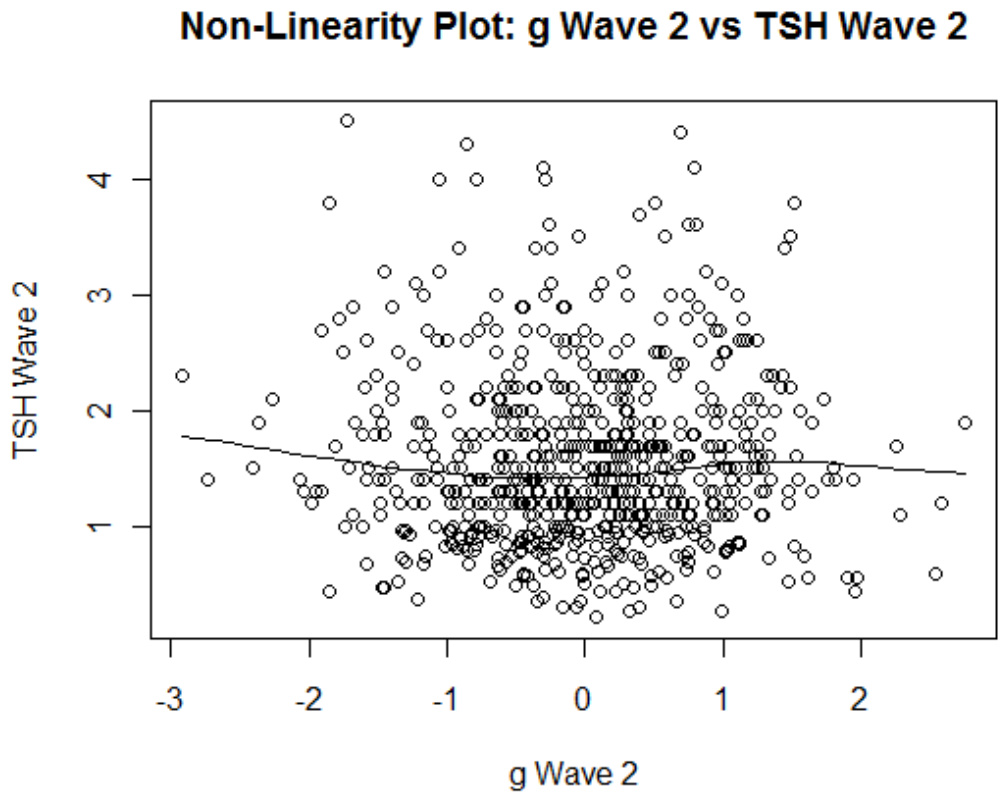
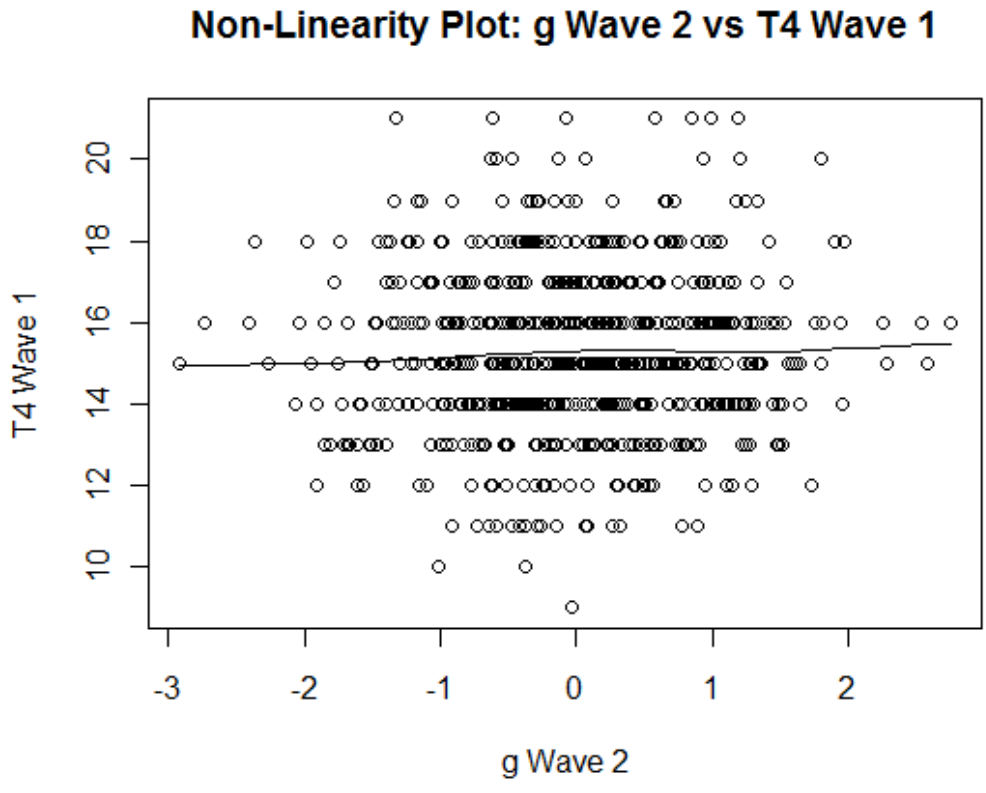


Figure S8:



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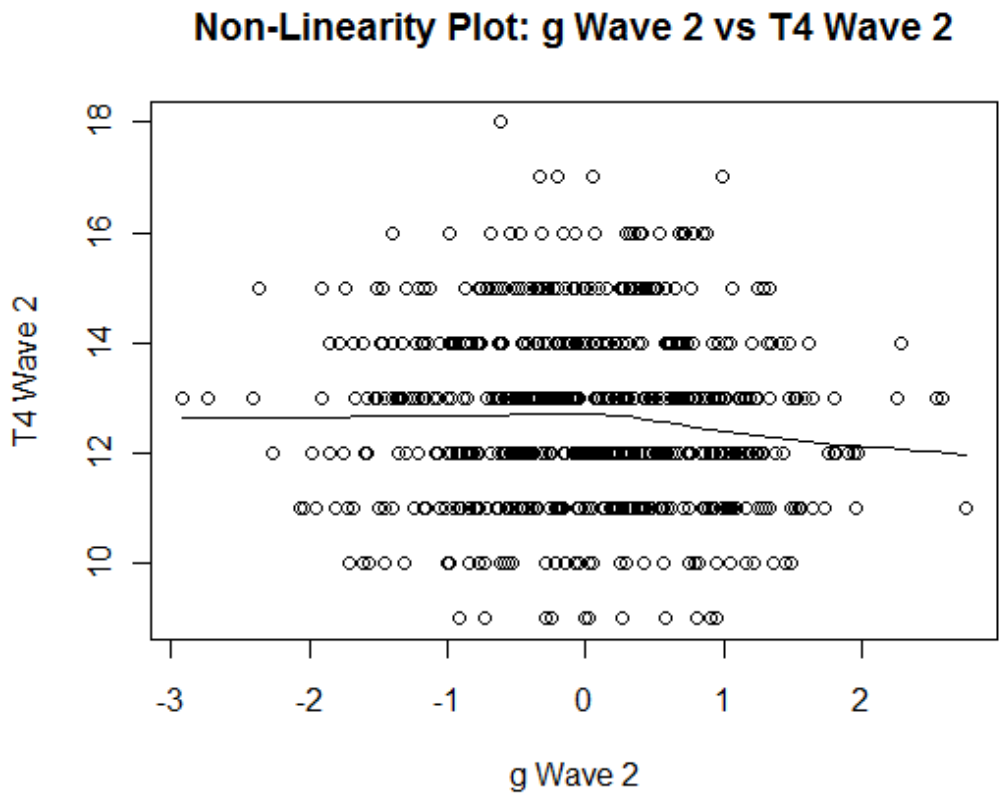

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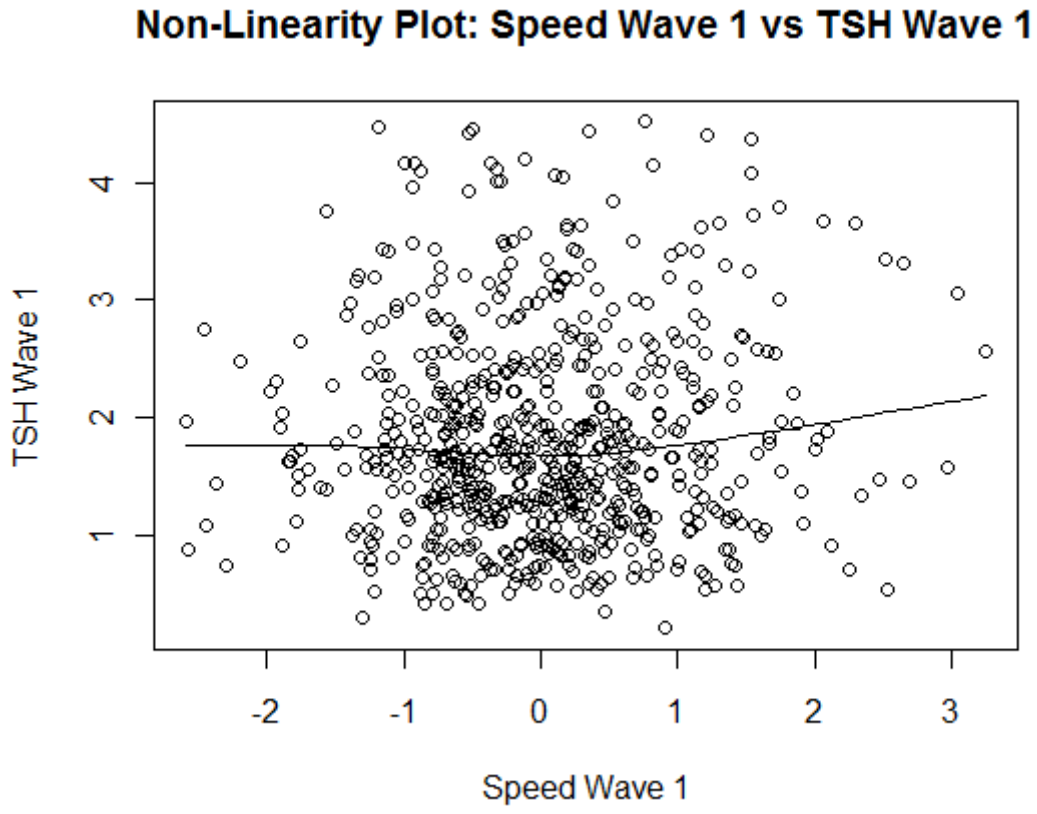

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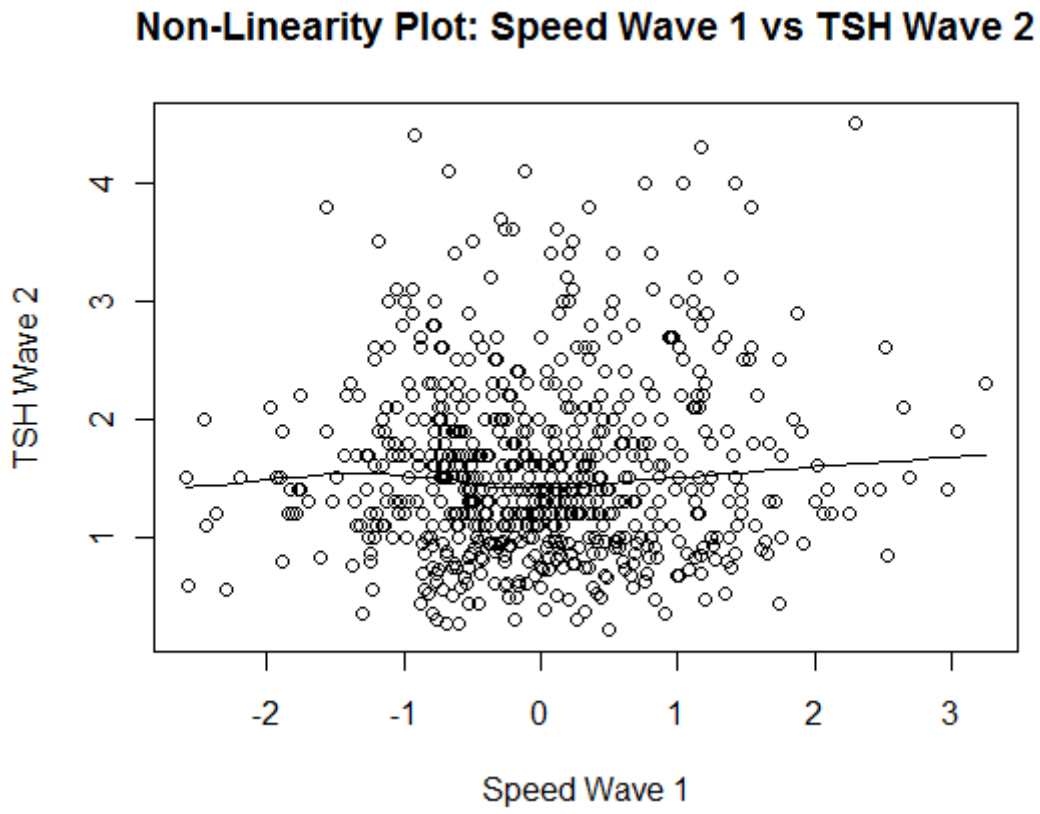

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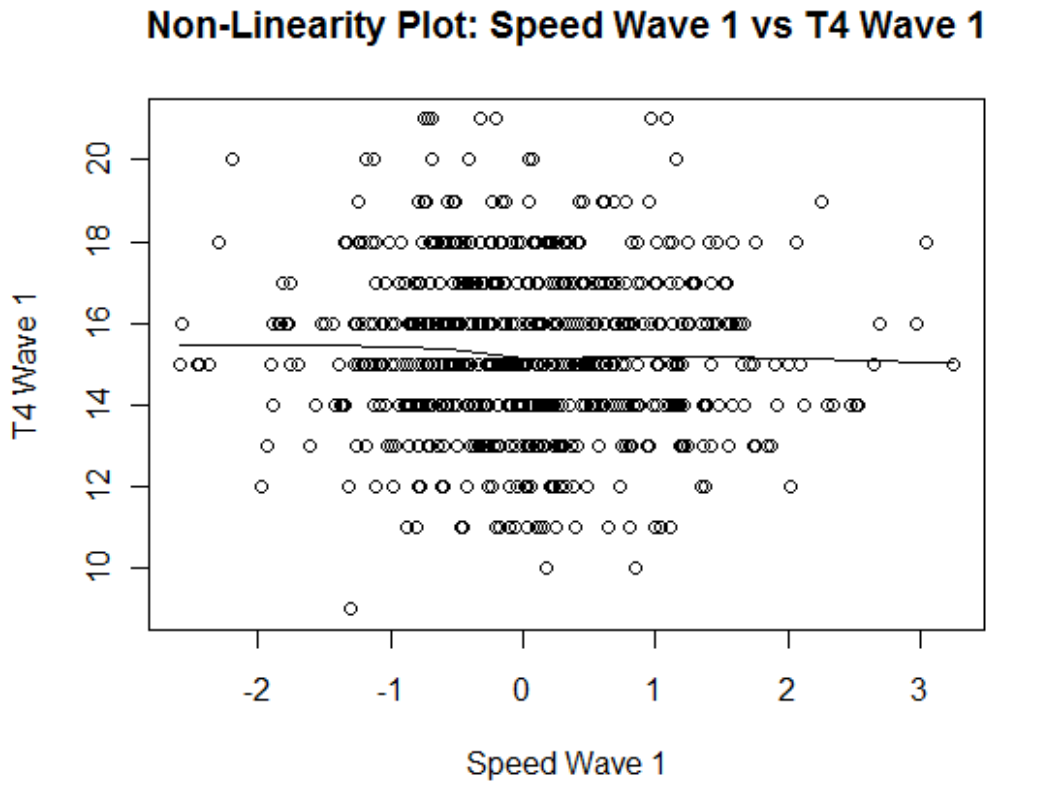

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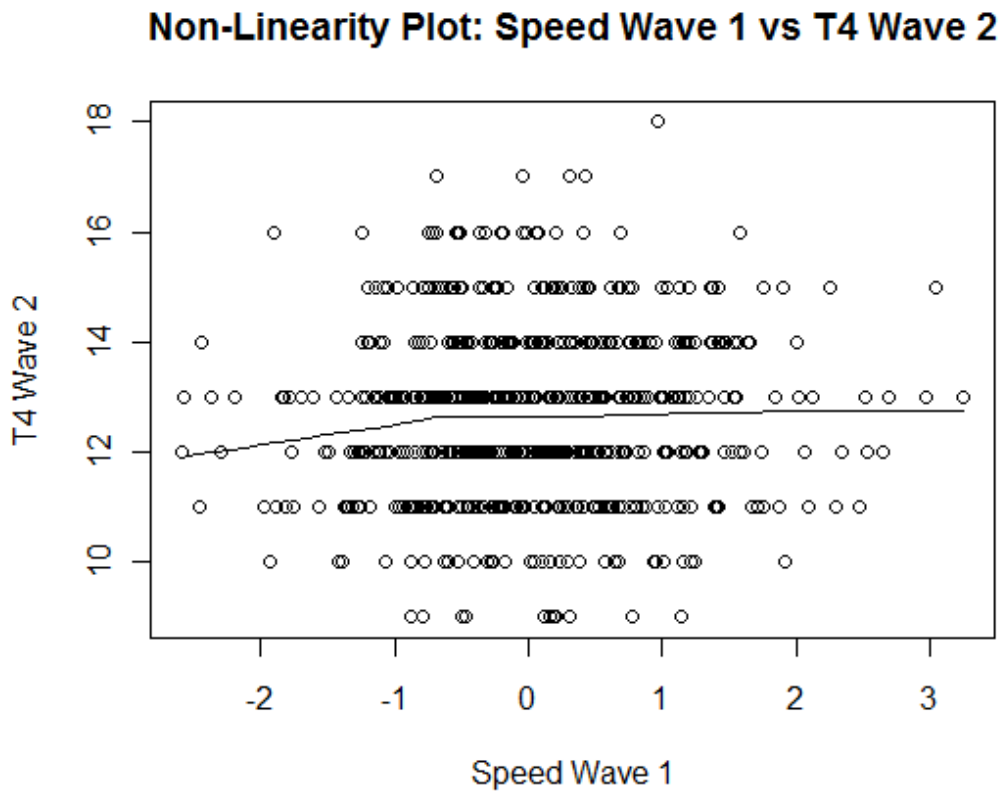

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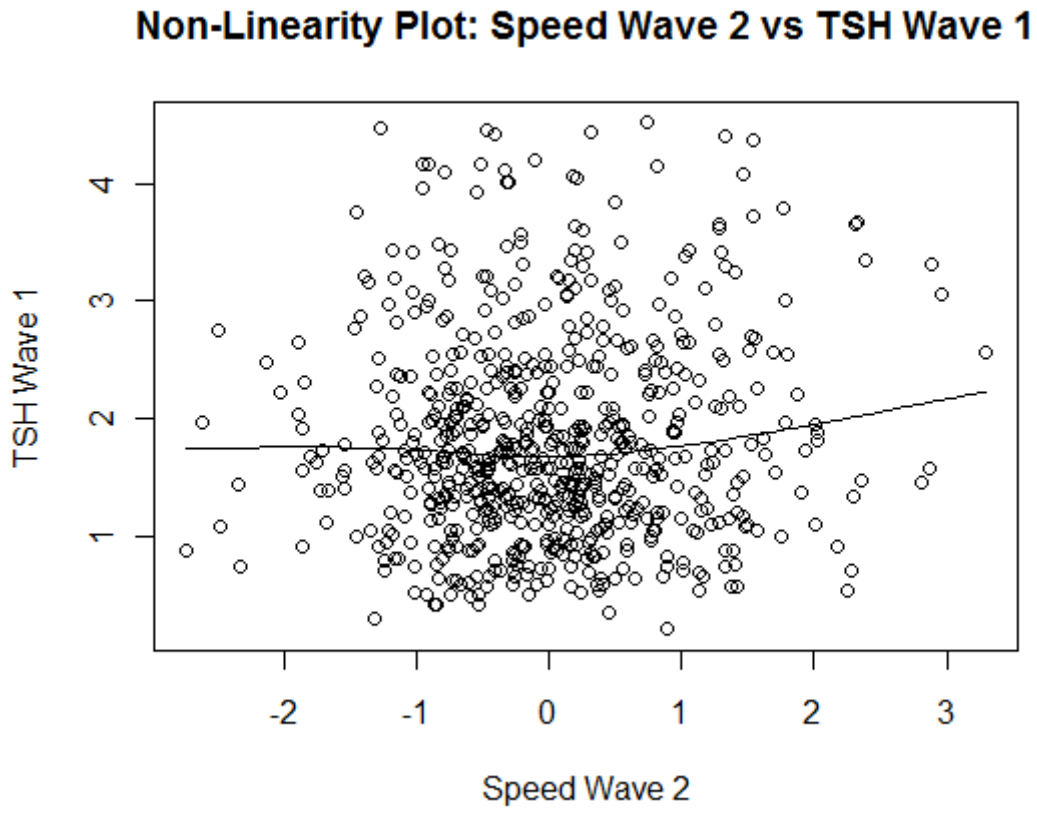

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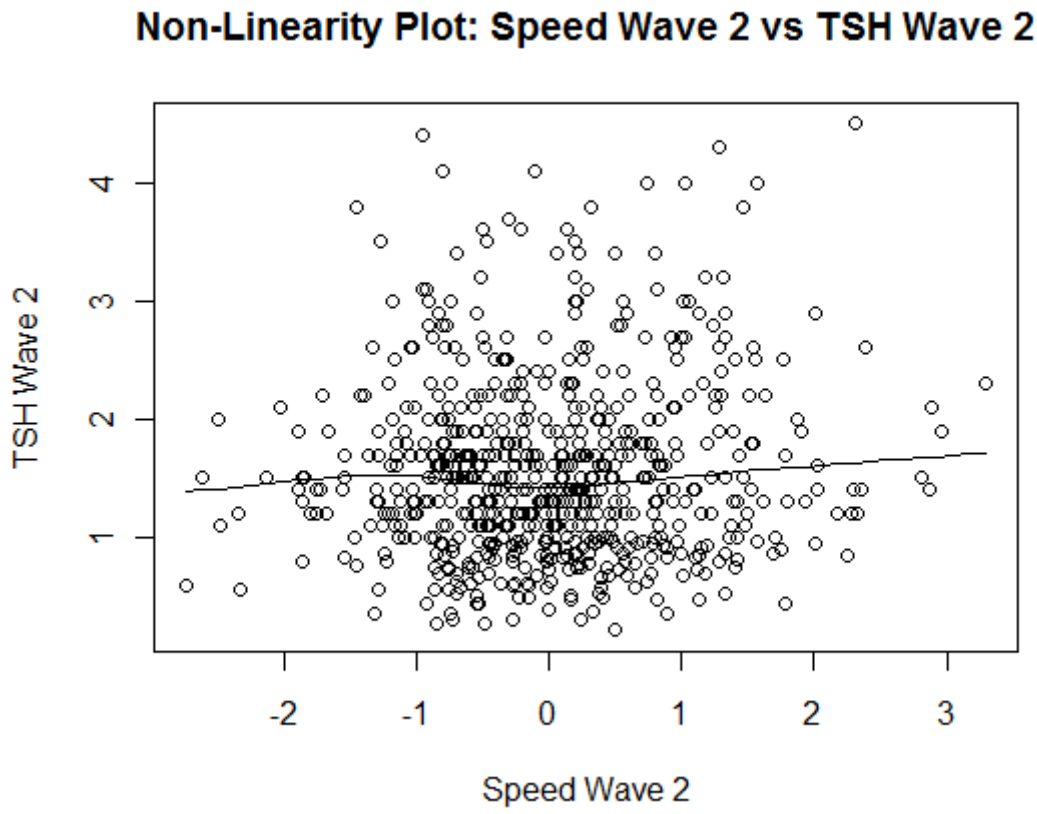

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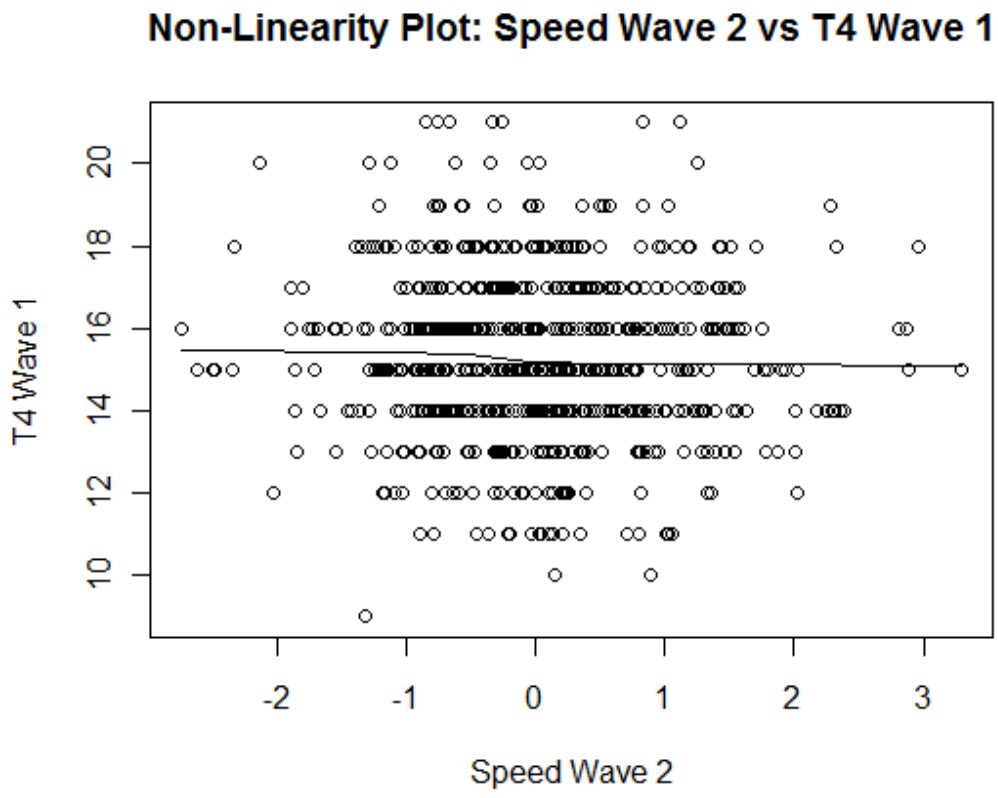

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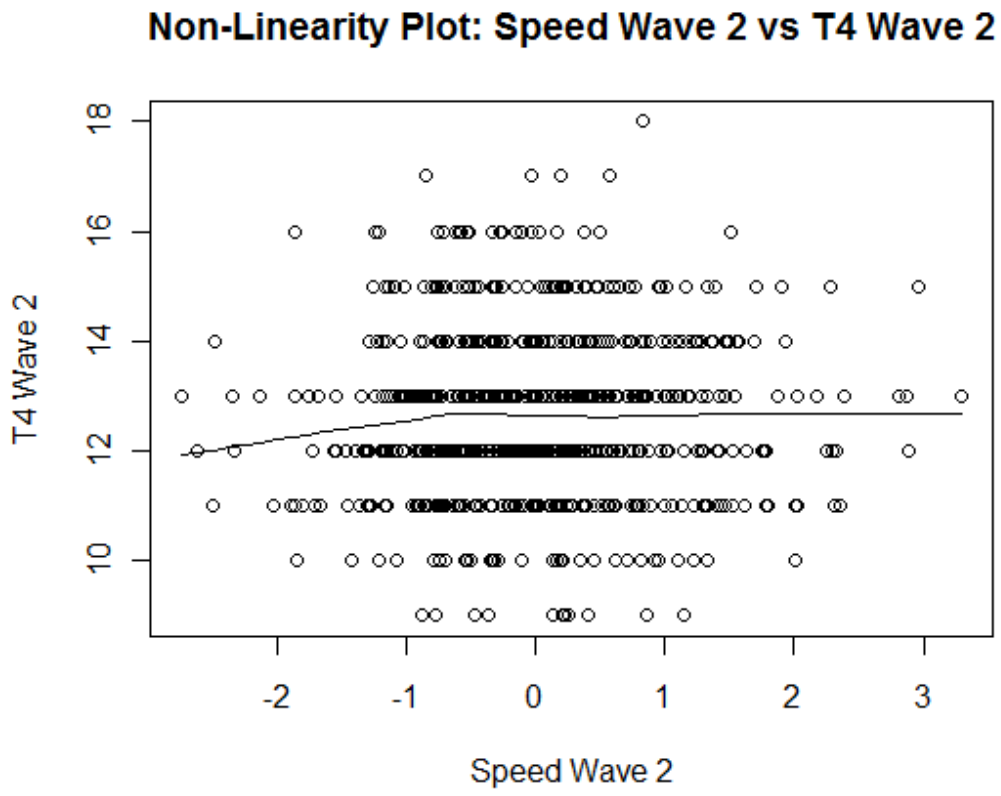

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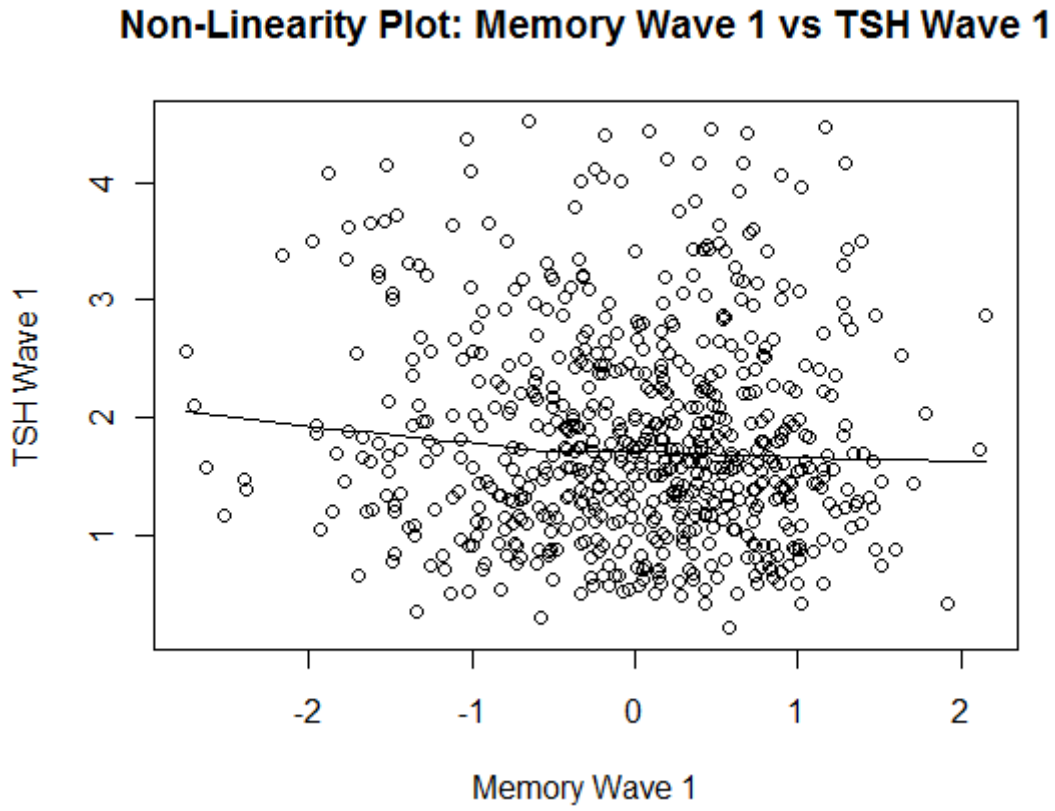

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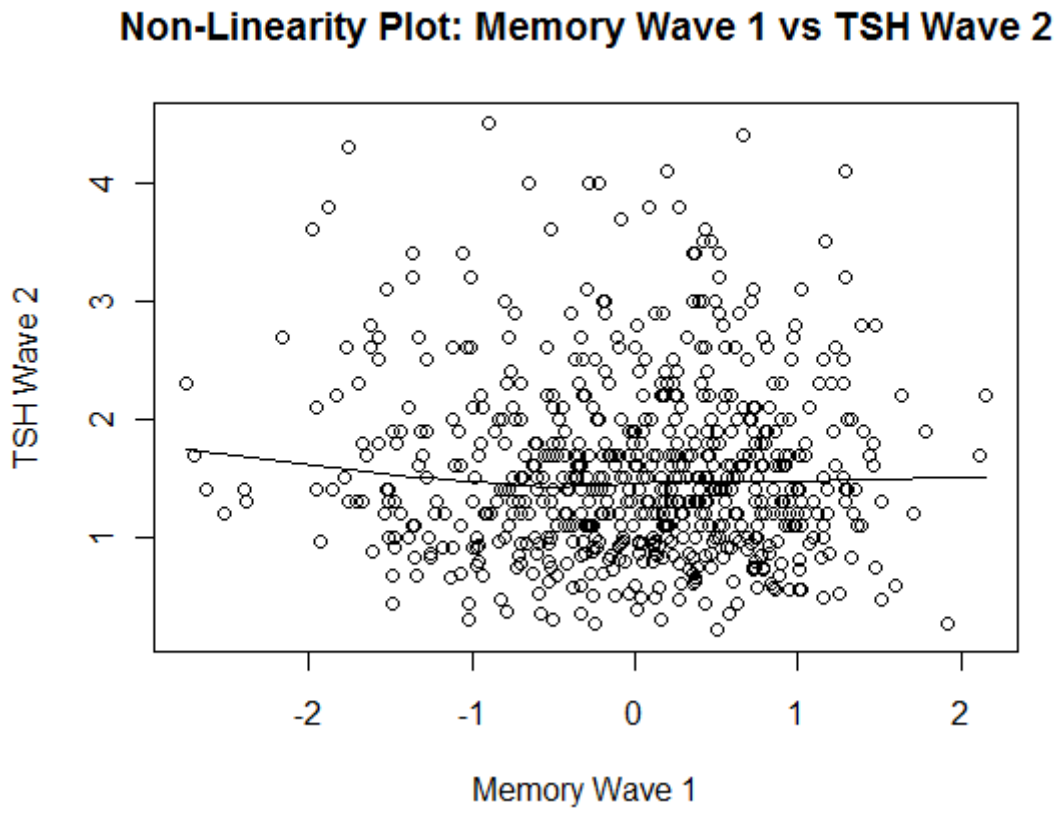

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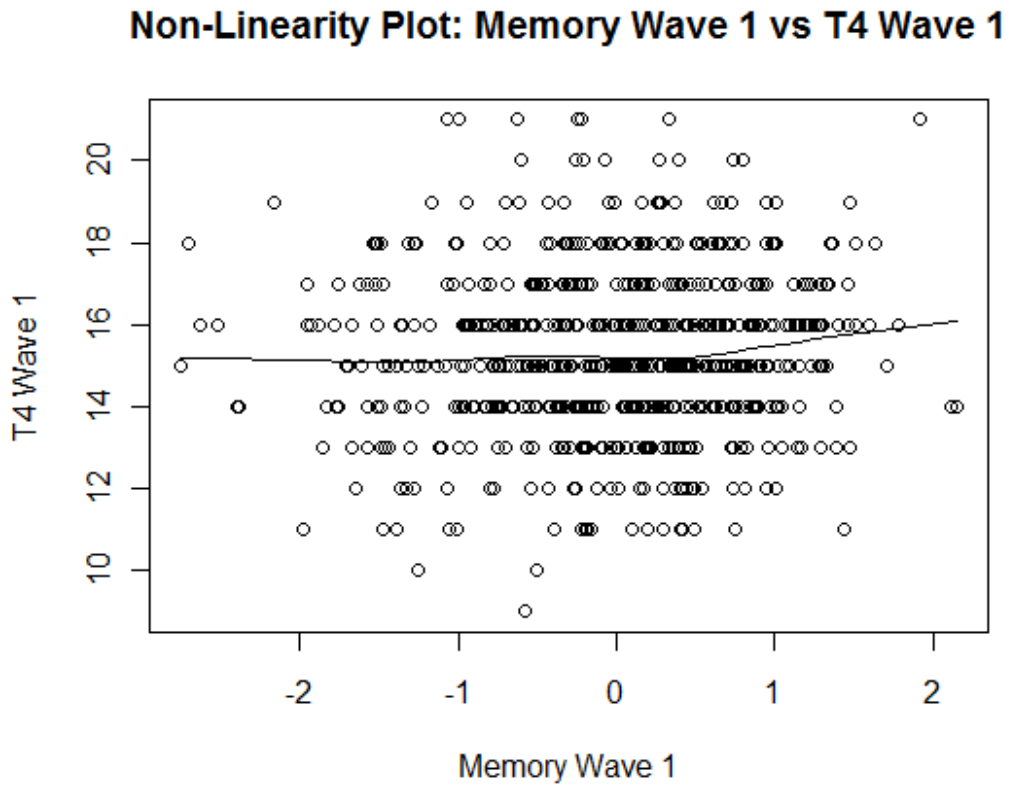

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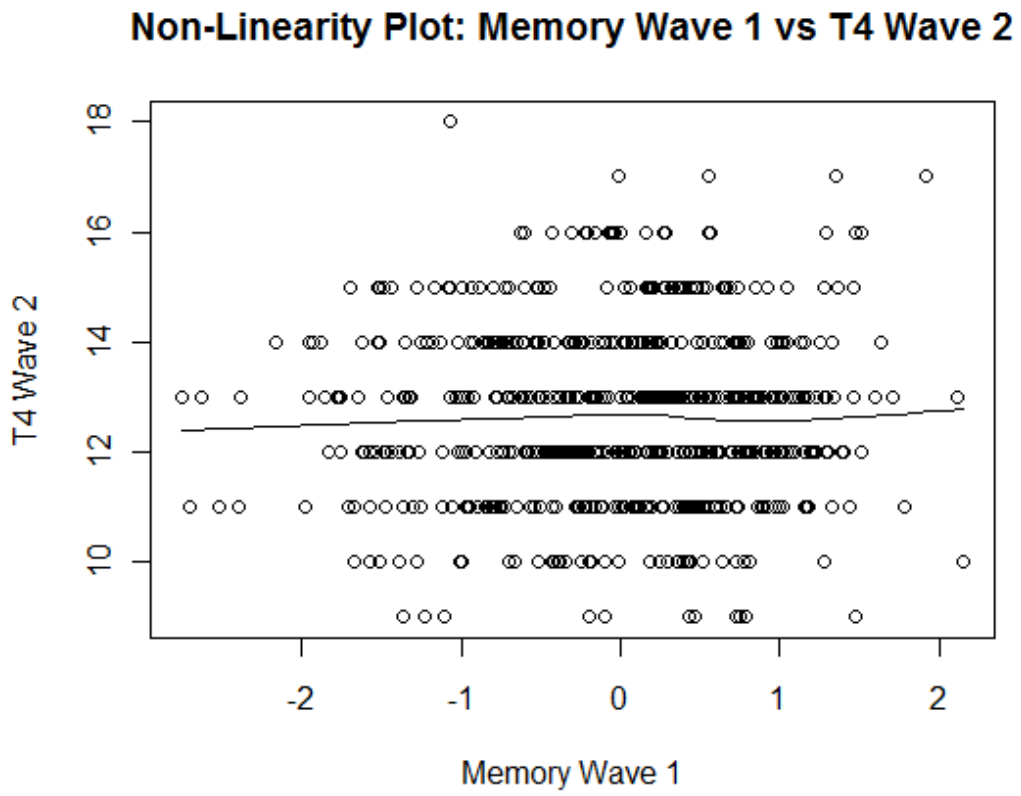
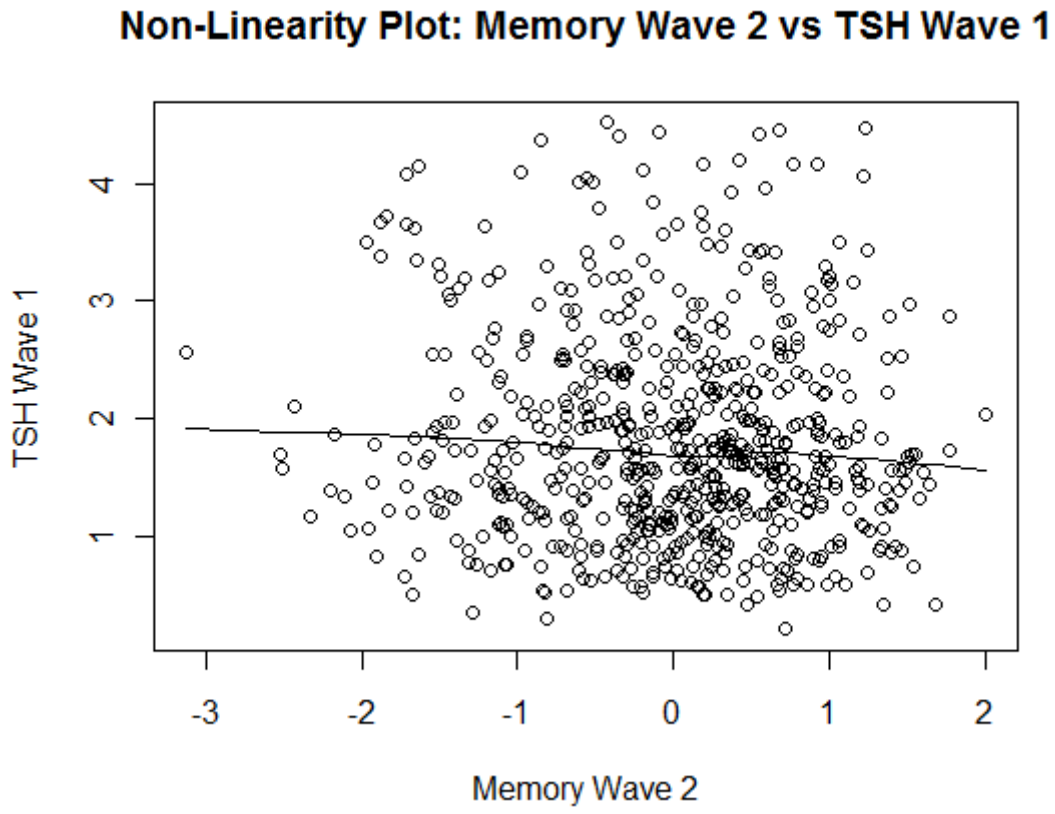


Figure S22:



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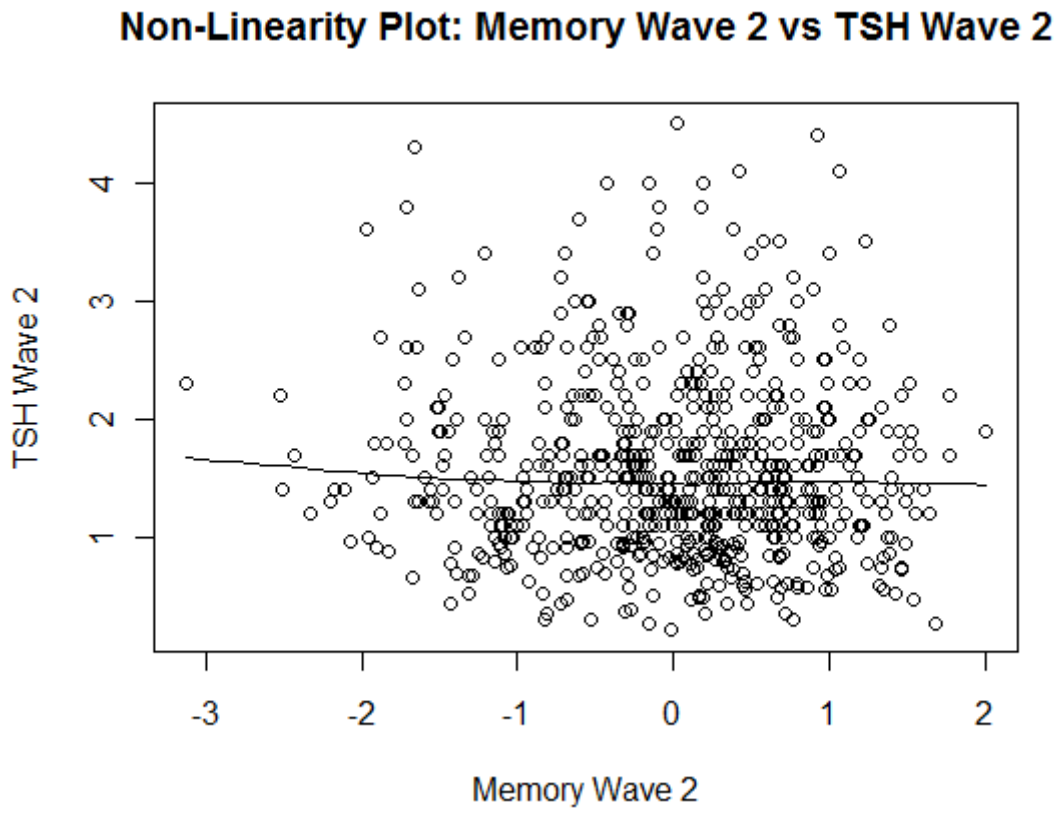

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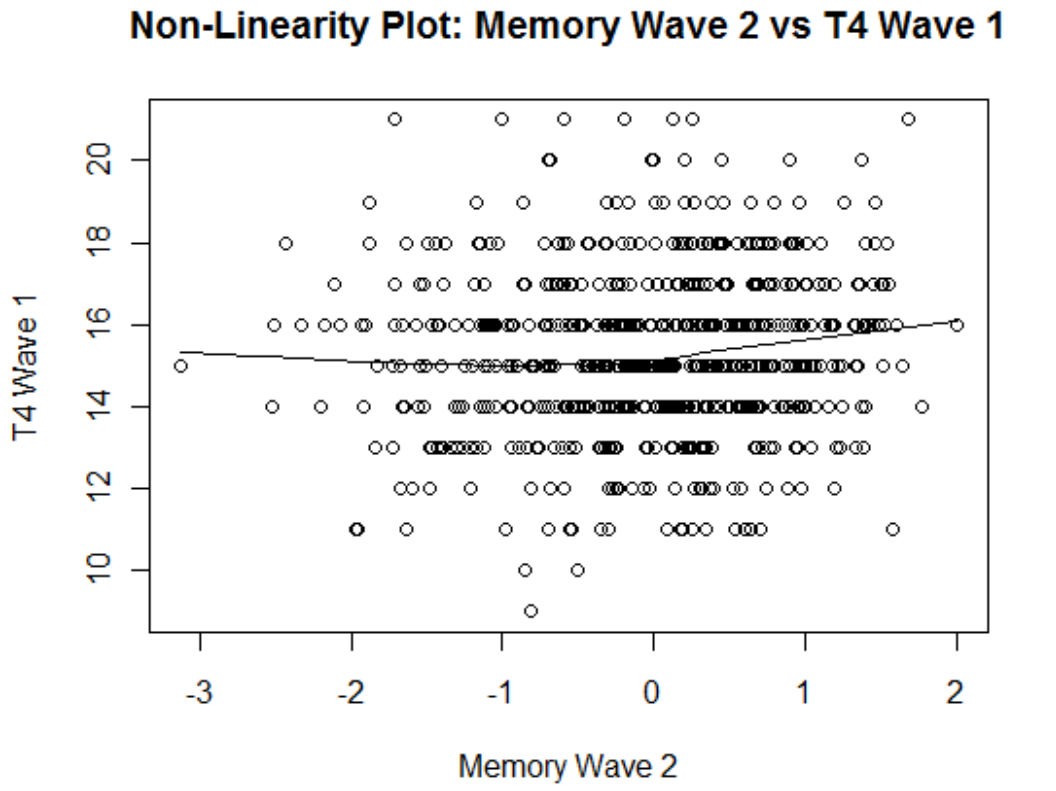

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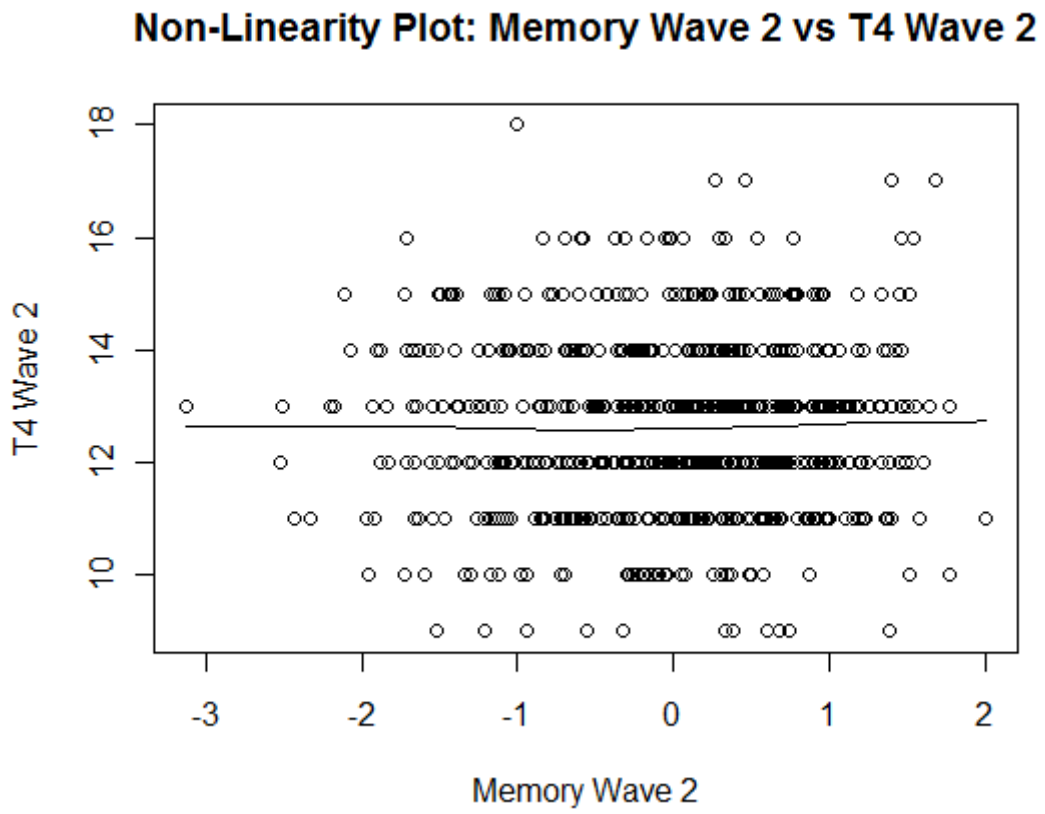
Non-Linearity Plot: Memory Wave 2 vs T4 Wave 2
T4 Wave 2
10
12
14
16
18
-3
-2
-1
0
1
2
Memory Wave 2

Supplementary Material C

Table S6:

Pearsons Correlations between TSH, T_4 and Individual Cognitive Ability Subscale Scores.

	Wave 1				Wave 2			
	Raw		Partial		Raw		Partial	
	TSH	T_4	TSH	T_4	TSH	T_4	TSH	T_4
WAIS-III^{UK}								
Digit Symbol	-0.03	0.07	-0.03	-0.03	-0.06	0.00	-0.03	0.00
Digit Span Backwards	-0.09*	0.01	-0.10*	-0.01	0.05	0.02	0.06	0.03
Block Design	0.02	0.06	0.01	0.04	0.02	-0.10*	0.02	-0.04
Letter-Number Sequencing	-0.08*	0.04	-0.09*	0.02	0.01	0.02	0.01	0.03
Matrix Reasoning	-0.03	0.05	-0.03	0.03	0.00	-0.04	0.00	0.01
Symbol Search	-0.03	0.05	-0.03	-0.01	-0.05	-0.02	-0.04	0.01
WMS-III^{UK}								
Logical Memory Immediate	-0.06	0.03	-0.06	-0.01	-0.07	0.01	-0.07	0.01
Logical Memory Delayed	-0.06	0.01	-0.06	-0.03	-0.05	0.03	-0.04	0.03
Verbal Paired Associates Immediate	0.07	-0.01	0.08	-0.02	0.06	0.03	0.07	0.02
Verbal Paired Associates Delayed	0.05	0.03	0.05	-0.01	0.04	0.01	0.06	-0.01
Spatial Span	-0.07	0.01	-0.07	-0.03	-0.03	-0.05	-0.03	-0.01
Speed Tests								
Simple Reaction Time	0.12**	-0.01	0.13**	0.00	0.07	0.10*	0.07	0.08*
Choice Reaction Time	0.02	0.03	0.03	0.05	0.07	0.03	0.06	0.01
Inspection Time	-0.06	0.03	-0.06	0.01	-0.05	-0.04	-0.05	0.00

* $p<0.05$; ** $p<0.01$; Raw correlations are uncorrected. Partial correlations are controlling for age, sex, HADS score and health covariates

Supplementary Material D

Table S7:

Cross-lagged Correlations between Cognitive Ability Latent Variables, TSH and T_4 in Split Samples by BMI and Drug Use

	1	2	3	4	5	6	7	8	9	10
1. TSH Wave 1	-	**0.76*** **	-	-	-0.07	-0.06	0.07	0.09	-0.09	-0.09
2. TSH Wave 2	**0.77*** **	-	-	-	-0.04	-0.01	0.08	0.08	-0.05	-0.02
3. T_4 Wave 1	-	-	-	**0.43*** **	0.08	0.05	-0.05	-0.06	0.05	0.10*
4. T_4 Wave 2	-	-	**0.43*** **	-	-0.05	-0.05	0.04	0.02	0.03	0.04
5. g Wave 1	-0.06	-0.03	0.07	-0.05	-	**0.98*** **	-	-	-	-
6. g Wave 2	-0.06	0.00	0.04	-0.06	**0.98*** **	-	-	-	-	-
7. Processing Speed Wave 1	0.06	0.06	-0.04	0.04	-	-	-	**0.98*** **	-	-
8. Processing Speed Wave 2	0.07	0.07	-0.04	0.02	-	-	**0.98*** **	-	-	-
9. Memory Wave 1	-0.07	-0.02	0.03	0.01	-	-	-	-	-	**0.86*** **
10. Memory Wave 2	-0.07	-0.01	0.07	0.00	-	-	-	-	**0.87*** **	-

Note: * $p<0.05$; ** $p<0.01$; *** $p<0.001$. All estimates shown in bold type are the wave 1 to wave 2 stability coefficients. Estimates below the diagonal are uncorrected associations having removed cases with BMI < 20. Estimates above the diagonal are uncorrected associations having removed cases taking a number of drugs known to influence thyroid hormone levels.

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Hu, L.T., Bentler, P.M. 1998. Fit indices in covariance structure modelling: Sensitivity to underparameterized model misspecification. Psychol Methods, 3, 424–453.

Hu, L.T., Bentler, P.M. 1999. Cut-off criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Modelling, 6, 1–55.

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Schermelleh-Engel, K., Moosbrugger, H., Muller, H. 2003. Evaluating the Fit of Structural Equation Models: Tests of Significance and Descriptive Goodness-of-Fit Measures. Methods of Psychological Research, 8, 23-74.